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Review Article

# Progress of the ALIFE2 study: A dynamic road towards more evidence

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ABSTRACT

Investigator-initiated studies are invaluable, especially in fields that are not particularly of interest for the pharmaceutical industry because they are either less profitable or concern special patient groups such as pregnant women. However, designing, conducting, and completing an investigator-initiated randomised controlled trial is challenging. Patients and physicians' preferences, ethics requirements, (international) legislation and funding are all areas where such challenges are encountered. The Anticoagulants for LIving FEtuses (ALIFE) 2 study (NTR3361) is an example of an investigator initiated international multicenter trial that progresses slowly, at least initially, as many challenges had to be overcome.

Here, we discuss the challenges we faced during the course of the ALIFE2 study up till now and we explain how some of these challenges can be tackled or even avoided.

## 1. Background

In April 2010, results of the Anticoagulants for LIving FEtuses (ALIFE) study were published [1]. A total of 364 women with unexplained recurrent miscarriage (i.e. in the absence of evident causes of miscarriage, such as abnormal parental karyotypes or uterine anomalies) was randomised to either low-molecular-weight heparin (LMWH) plus acetylsalicylic acid (ASA), ASA alone or placebo (for ASA). The results indicated that neither the combination of LMWH and ASA, nor ASA alone improved the likelihood of live birth in a subsequent pregnancy. Supported by data from two similar studies published around the same time, these results changed guideline recommendations and influenced clinical practice [2–4].

Although evidence for the lack of efficacy of anticoagulants in women with unexplained recurrent miscarriage was provided by these three independent studies, the question remains whether the subgroup of women with recurrent miscarriage and inherited thrombophilia may benefit from anticoagulants during pregnancy [5]. The association between inherited thrombophilia and pregnancy complications was previously investigated [6,7]. Homozygosity for Factor V Leiden or heterozygosity for the prothrombin 20210A mutation were found to have a significant association with early pregnancy loss, whereas late pregnancy loss was most strongly associated with protein S deficiency and heterozygosity for either Factor V Leiden or the prothrombin 20210A mutation. In parallel, women with *acquired* thrombophilia, i.e. the presence of antiphospholipid antibodies, are at an increased risk of recurrent miscarriage and other pregnancy complications [8,9]. As anticoagulants increase the chance of live birth in women with *acquired* thrombophilia, physicians are tempted to extrapolate this to women with inherited thrombophilia, and prescribe LMWH, ASA or both [10,11]. However, a beneficial effect has not been proven for these women. A subgroup analysis of 47 women with inherited thrombophilia in the ALIFE study suggested a beneficial effect of LMWH plus ASA (relative risk of live birth 1.31, 95% confidence interval [CI] 0.74 to 2.33) and of ASA alone (relative risk of live birth 1.22, 95% CI 0.69 to 2.16). This analysis was underpowered to demonstrate an effect and results of our systematic review further underlined the lack of data in this particular group of women [5]. A recent meta-analysis of eight trials comparing LMWH to no LMWH during pregnancy in women with inherited thrombophilia, also including data from the ALIFE study, found no significant difference in pregnancy loss rates between the LMWH and no LMWH treatment groups (relative risk 0.81, 95%CI 0.55 to 1.19) [12]. This point estimate favoring LMWH was lost if only multicenter studies were included in the meta-analysis (relative risk 1.04, 95%CI 0.93 to 1.16).

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Treatment with anticoagulants may increase the risk of bleeding in pregnancy or around delivery. Furthermore, it is burdensome, requires daily subcutaneous injections and often causes delayed-type hypersensitivity skin reactions, itching and/or bruises [13,14]. Therefore, evidence to justify anticoagulants for women with inherited thrombophilia and recurrent miscarriage is urgently required. Hence, results from the currently ongoing ALIFE2 study, in which the effect of anticoagulants on live birth in women with recurrent miscarriage and inherited thrombophilia is evaluated, are anxiously awaited.

The importance of evidence obtained from randomised controlled trials is undeniable and widely recognized. But conducting a clinical trial involves time and effort and can be challenging at times. As for most international multicenter investigator-initiated trials, the journey from the drawing board to the actual set-up of the trial has been far from a smooth ride and various obstacles had to be overcome. Identifying and finding a solution for these obstacles has been key in improving the recruitment rate. Here, we will discuss several of the obstacles encountered for the ALIFE2 study and how they have been tackled.

## 2. Experienced challenges and hurdles

### 2.1. Design, set-up and funding

The ALIFE2 study was designed with much attention to methodological aspects, such as the number and timing of previous miscarriages (determining eligibility), the study design (a two- or three-armed trial, open label or placebo-controlled), the trial intervention (LMWH, ASA or both and dose thereof) and start of the intervention (pre- or post-conceptional). The study proposal was subsequently presented to national and international experts in the field to further optimize the design and also to raise interest for the study amongst colleagues, who would later be requested to participate in the study.

The final study protocol is a two-armed, open-label randomised controlled trial, in which pregnant women with two or more miscarriages (not necessarily consecutive and irrespective of timing of the pregnancy loss) and inherited thrombophilia (Factor V Leiden, prothrombin G20210A mutation, or deficiency of protein C, S or antithrombin), are randomised before the 7th week of pregnancy to either LMWH (enoxaparin 40 mg or equivalent dose of another LMWH, once daily), or no intervention [15].

The primary efficacy outcome of the study is live birth, and secondary outcomes include bleeding, venous thromboembolism (VTE) and obstetric complications [15].

Initial limited funding was acquired as part of a VIDI-grant (The Netherlands Organization for Health Research and Development, 016.126.364). Additional funding was acquired by the UK (United Kingdom) team from the University of Warwick as part of a Research for Patient Benefit grant (RfPB) from the UK National Institute for Health Research (NIHR) [PB-PG-1013-32011].

Compared to the previous ALIFE study - a national, multicenter trial -, we anticipated recruitment to be more challenging because of the restrictive inclusion criterion of the presence of inherited thrombophilia in women with recurrent miscarriage. As inherited thrombophilia tests are positive in approximately 15% of women with unexplained recurrent miscarriage, it was estimated that completing enrolment with the required 400 women would be accomplished within 5 years, with continued follow-up until the outcome of pregnancies 9 months after inclusion of the final study participant. For a detailed overview of the study protocol and sample size considerations, we refer the reader to the open access published ALIFE2 study protocol [15].

### 2.2. Inclusion and exclusion criteria

Definitions and nomenclature of recurrent miscarriage, including timing of miscarriage, number of losses and whether or not the losses were consecutive, vary widely internationally [16–18]. Although the choice of two miscarriages as a diagnosis of recurrent miscarriage and as the inclusion criterion for the study was criticized in the design phase of the study, this did not lead to substantial delay or disagreement once the protocol was finalized. Different views of colleagues regarding this criterion were respected, as these merely reflect the lack of strong evidence for either definition. Clarification of the rationale behind investigators' opinions appeared key in realizing a compromise of including women with two or more, not necessarily consecutive, miscarriages. With proper explaining and reasoning, the use of different definitions did not affect recruitment. The broad definition of recurrent miscarriage used in the study (i.e. two or more miscarriages) enables participation of clinics with a stricter definition of recurrent miscarriage (i.e. three or more) to participate. An open discussion regarding the definition is essential to create mutual understanding and positively influence study participation.

### 2.3. Choice of study intervention

In the ALIFE2 study, enoxaparin 40 mg injection once daily (or an equivalent dose of another LMWH), is compared to standard pregnancy surveillance (no intervention). The type of treatment and dose were extensively discussed. A three-armed trial also including ASA was not considered feasible as the number of participants needed would increase from 400 to over 700.

For heparin, both the anticoagulant activity and anti-inflammatory properties are thought to contribute to maintenance of pregnancy [19]. In addition, heparin promotes trophoblast differentiation in vitro [20]. For ASA, the mechanism of action in pregnancy is less clear. Unfractionated heparin needs to be administered at least twice daily, whereas for LMWH a single daily dose is sufficient. As in a direct comparison of LMWH and UFH (both combined with ASA, in women with antiphospholipid syndrome) both appeared equally effective, LMWH was considered more favorable than UFH [21]. Results of the previously mentioned subgroup analysis in women with inherited thrombophilia in the ALIFE study suggested a greater effect on live birth of LMWH plus ASA when compared to ASA alone. Furthermore, for women with antiphospholipid syndrome, there is no evidence that ASA alone increases live birth rates after recurrent miscarriage [5]. This knowledge, taken together with the fact that for clinical practice the question whether LMWH is effective appears most pressing, led to LMWH as the intervention of choice for the ALIFE2 study.

Enoxaparin 40 mg or an equivalent was the dose decided upon after consultation with many colleagues; both to verify that there was agreement amongst peers on the scientific merit of the study, as well as to make sure that colleagues would be willing to participate. The clinicians' experience and/or preference as well as the availability per type of LMWH may differ per country and the possibility to use different types of LMWH within study context allows for an easy switch to another LMWH in case of side effects or logistics. Consensus on the dose was not easily reached. A high dose (e.g. equivalent to or even higher than 80 mg enoxaparin) would infer a higher bleeding risk, but would minimize the possibility that a (dose-dependent) beneficial effect of LMWH would not become apparent in the trial. Using a low dose would conversely be potentially associated with a lower bleeding risk, but a negative trial outcome (i.e. no beneficial effect of LMWH) would not settle the doubt that a higher dose could have been effective. However, the LIVE-ENOX trial showed no additional benefit of 80 mg enoxaparin over 40 mg enoxaparin in women with recurrent miscarriage [22].

### 2.4. Control group and concomitant medication

In the ALIFE2 study LMWH is compared to standard pregnancy surveillance (no treatment). The use of a placebo (e.g. saline injections) was considered in the design-phase. Compared to no treatment, placebo use could affect participation positively as well as negatively, as both a

50% chance of saline injections, as well as a 50% chance of open-label no treatment may be reasons for women to refuse or cancel participation. An example of a successful randomised double-blind placebo-controlled trial in the pregnant population was the recent PREFIX study; a clinical trial evaluating enoxaparin for prevention of recurrent miscarriage in nonthrombophilic women in 13 French hospitals [23]. Arguments in favor of a placebo-control include a potentially more valid trial result and minimization of the risk of performance bias, i.e. that systematic differences arise between the groups in the care that is provided, in exposure to other factors, and in assessment of data including bleeding [24]. The difficulties of manufacturing placebo injections and the high costs associated with manufacturing and distribution were the most important arguments against the use of placebo. An open-label design with standard pregnancy surveillance (no treatment) as a comparator to LMWH was agreed upon, as for the unequivocal primary outcome (live birth) a placebo effect was considered minimal. Furthermore, the protocol accounted for the important quality criterion of concealment of allocation [25].

In the initial protocol, the use of medication with anticoagulant effects such as non-steroid anti-inflammatory agents and ASA was prohibited. This was amended 19 months after the start of the trial, after an eligible woman with a history of pre-eclampsia was not included because her treating physician wanted to prescribe ASA to reduce the risk of pre-eclampsia in her subsequent pregnancy. A head to head comparison of LMWH versus no treatment, not contaminated by any co-medication, will provide the most valid evidence. However, with already few eligible patients we considered it undesirable that eligible women would be excluded for this reason. As the number of included women with a history of pre-eclampsia was anticipated to be low and ASA use would be randomly distributed between the two treatment groups, the scientific integrity of the trial did not appear to be jeopardized, the protocol was amended as such: “Apart from the assigned study medication, women are strongly discouraged to use anticoagulants or other medication that affects hemostasis, including non-steroidal anti-inflammatory drugs (NSAID's)”.

At a low dose (≤150 mg daily), ASA to lower the risk for recurrent pre-eclampsia (at the discretion of the treating physician) is discouraged but allowed. This is an example of how protocol amendments can lead to increased enrolment, without compromising the validity of the study.

### 2.5. Review board approval and multicenter dimensions

With the foundation for the design of the study laid amongst Dutch and international colleagues, it was anticipated that the study could be initiated in the principal center, (Amsterdam University Medical Centers – location Academic Medical Center [AMC], the Netherlands) and shortly thereafter in the other Dutch centers, where colleagues had expressed their intention to participate. Unfortunately, reality proved otherwise. First, the study had to be approved by the ethics committee of the AMC. After initial submission on June 20th 2012, approval was obtained on August 31st 2012 and a subsequent notification of no objection by the competent authority was obtained on November 12th 2012.

In the Netherlands, a new directive had just been installed, intended to improve and speed-up medical-ethical review of multicenter studies [26]. Whereas previously a new study protocol would have to pass the review board of each participating center, this directive states that the individual review boards in the Netherlands are all officially acknowledged and that a positive decision of either one is applicable to all centers. Once reviewed and approved by one ethics board, the execution of the study in another center should only be agreed upon by the local board of directors. This appears a straight-forward procedure, which according to an observational study decreased the median time to approval from 118 days in centers that did not comply with the directive, to 50 days in centers that did. In practice, however, the boards did not comply with this new directive, and would not consent without a full review of the submission by their own ethics board, which resulted in substantial delays [27,28].

Initiating participation of an additional not initially listed center thus implied collecting the necessary documents from the trial office or lead physician concerned at that new center (varying between 3 weeks to several months), a request for ethical approval (typically obtained in 2 weeks), a request for board of directors' approval at the new center (varying between 1.5 to several months) and preparing the initiation of the study at the new center (1 week), proved to be extremely slow.

These multicenter dimensions become even more challenging when international centers become involved. Additional funding is required, local standard practice can differ from the initiating country, other legal regulations apply and obtaining local ethics approval is subject to other matters and restrictions than already encountered. On the other hand, international participation will maximize recruitment and will potentially increase the external validity of the study, as women with different backgrounds, ethnicity and cultures can be enrolled.

A great number of international colleagues were supportive regarding the ALIFE2 study. However, in parallel to the Netherlands, several centers initially willing to participate, withdrew later; still supportive of the study, but not able to or willing to cope with anticipated initiation difficulties. It is therefore again key to ensure commitment of the center intended to participate in an early stage, before time and effort are wasted if initially consenting partners refrain from participation in a later stage. However, for those centers willing to participate, perseverance will pay off in the end. With different authorities and logistics involved, the road from pledging to participate to local ethics approval to the actual first randomisation may take time in our experience.

A new European regulation (no. 536/2014) installed with the aim to harmonize assessment of applications for clinical trials was published in May 2014 and was put into effect mid-2016 [29]. It states that the medical and scientific aspects of the application will be jointly assessed by all member states via one application, which has been a major improvement in the application procedure for new trials. However, as national aspects such as privacy, insurance and research facilities of the application still need to be assessed by each member state individually, and local management boards of the centers should still approve the execution of the study, this regulation may be subject to the same pitfall as the Dutch directive. In any case, patience and persistence are essential and will be rewarded.

### 2.6. Conducting research in the pregnant population

Pregnant women are considered a special population and the need to obtain data on safety and efficacy of medication in pregnant women from clinical trials is undeniable [30,31]. Counselling eligible patients for the ALIFE2 study, in which the comparator arm is standard pregnancy surveillance (i.e. no intervention), can be challenging in women who have already experienced at least two prior pregnancy losses and are understandably adamant on preventing a subsequent miscarriage. Careful explanation of what is already known on the topic, but more importantly what evidence is still lacking, has proven to be essential. Additionally, a close collaboration between treating physician, midwives and the pregnant women participating in the study has led to very few patients being lost to follow-up in the ALIFE2 trial. In the UK an additional challenge has been the thromboprophylaxis risk assessment that is done at 28 weeks in routine antenatal care as per RCOG guidelines (https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf). This has meant some women randomised to standard care are given LMWH after 28 weeks. As the majority (99%) of pregnancy losses would have occurred before 28 weeks, that administration of LMWH after 28 weeks will have little effect on the primary outcome of live birth rate. The data analysis will be intention to treat so those randomised to standard care, but receiving LMWH from 28 week will remain in the standard care arm.

### 2.7. Factors influencing actual recruitment

Once a center can start recruiting, the actual inclusion rate is dependent on the input and efforts of local investigators and trial nurses, who are often engaged with multiple studies and clinical work. Research has shown that the only factor truly contributing to recruitment is a dedicated local principal investigator or dedicated research staff who are convinced of the value of recruitment for clinical practice [32]. Trial recruitment remains a complex process and considerable variation in recruitment and retention rates in publicly funded trials has been described previously [33]. An open trial design and reminding non-responders by telephone were found to increase recruitment rates in a recent Cochrane review, whereas optimizing the patient information form had little or no effect on recruitment [34].

Here, the discrepancy between commercial pharmaceutical trials and investigator-initiated studies such as ALIFE2 become apparent. Pregnant women are often excluded from pharmaceutical trials because of the pharmaceutical companies' concerns for liability.

This implies that the great majority of studies undertaken in pregnant women are investigator-initiated and the academic sponsors have to bear the expenses of the high liability insurance fees. A pharmaceutical trial can provide recruitment fees as high as several thousand euros per included patient, whereas the ALIFE2 study only offers an inclusion fee of €250,- per completed case report form. This compensation for the work of study personnel per randomised patient is far too small to be considered as an incentive to take charge and proactively recruit patients, or exploit trial coordination or reporting activities. The inclusion rate of the study is therefore merely dependent on the commitment and scientific enthusiasm of local investigators. With high (clinical) workloads and numerous studies demanding efforts ALIFE2 is not always top priority. Study organizers therefore need to realize that identifying centers with dedicated (principal) investigators or trial offices as potential participating centers is very important.

In Netherlands each site interested to participate in the study, was asked to estimate the number of anticipated inclusions per year. In the UK we asked each site to complete a feasibility questionnaire and estimate the number of positive inherited thrombophilia screens they had per year. This approach has proven to be problematic because the clinicians at the sites did not have access to this data and their estimates were inaccurate.

However, newly started trials are often subject to the paradox that once a trial has begun, the number of eligible patients is suddenly much lower than the number initially anticipated. This phenomenon is known as Lasagna's law, and appears to hold true for ALIFE2 as well [35]. We observed considerable time between the date the site was activated and the date of the first patient enrolled, varying from 6 months to almost 2.5 years.

In the end of 2014, the results of the Thrombophilia in Pregnancy Prophylaxis Study (TIPPS) were published. This was a multicenter open label randomised trial that recruited 292 women with thrombophilia (inherited or presence of antiphospholipid antibodies) who were at an increased risk of VTE or placenta mediated complications. The rates of pregnancy loss were similar in the dalteparin treated group (12 of 146 [8.2%]) and the no dalteparin group (10 of 143 [7.0%]), with a risk difference of 1.2% (95% CI -4.9 to 7.3) [36]. Although the ALIFE2 study is markedly different, one might speculate that the results of this study may have temporarily damped investigator enthusiasm. Reassuringly, we have noticed increased international interest in the study over time, with the number of participating centers continuously expanding. Needless to say, as many women with inherited thrombophilia and recurrent pregnancy loss are prescribed LMWH in absence of evidence and outside study participation, both “positive” as “negative” results of the ALIFE2 will be of invaluable significance to clinical practice.

The Women and Child Health Research Consortium initially established in 2003 after a grant from The Netherlands Organization for Health Research and Development, is a renowned collaborative initiative for multicenter research in the Netherlands. Since 2015, the consortium is under the auspices of the Dutch Society of Obstetrics and Gynecology. Over 70 medical centers have joined this initiative, which provides unique logistics for the ALIFE2 study. Joining centers are accustomed to including patients in ongoing investigator-initiated studies. Furthermore, results of consortium studies find their way to daily practice more easily. However, the popularity of this network may outgrow its capacity. With a limited number of trials, the collaborators were dedicated to deploy themselves for others, but as more and more investigators wish to benefit from the network and progressively more studies are introduced, the network is at risk of becoming overstrained and participants' focus returns to individual priorities rather than those of the collaboration. This is a disadvantage for investigator-initiating studies compared with pharmaceutical trials. It can be overcome by an enthusiastic approach, involving education (making collaborators aware of the need for enrolment, providing them with tips for execution of the study), motivation (providing progress reports encouraging contribution and possible addition of sub study questions) and help with identifying barriers that are experienced in the local setting. However, only such a continuous effort will render the study staying on top of priorities. A reorganization of the Consortium in 2016 aimed for a more efficient collaboration, but infers higher overhead costs for participating studies.

### 2.8. Discrepancy between scientific evidence and current clinical practice

Although current guidelines state that there is no evidence of a beneficial effect of LMWH on live birth in women with recurrent miscarriage and inherited thrombophilia and that treatment is burdensome, expensive and associated with bleeding, some physicians tend to employ a benefit-of-the-doubt practice and prescribe LMWH to their patients [4,37–39]. However, LMWH should not be prescribed in women with inherited thrombophilia for prevention of recurrent pregnancy loss, as there is currently no evidence to support this practice [12]. No recruitment or selective recruitment (only randomizing women at perceived ‘low risk’, and routine prescribing LMWH to others) does not serve the study and will not provide the evidence needed. Furthermore, this practice provides women who are randomised to no treatment with an opt-out option, securing their LMWH prescription elsewhere. Education, counselling and discussing the different viewpoints regarding evidence is again key to overcome this issue.

A problematic aspect is the cost of screening for inherited thrombophilia. With no currently known effective treatment leading international guidelines advise against thrombophilia screening in women with recurrent pregnancy loss, unless in the context of research [38,39]. These guidelines and recommendations on thrombophilia screening changed over the course of the ALIFE2 study. Although the research exception is explicitly stated this has strongly affected recruitment rates for the ALIFE2 study, as thrombophilia screening is no longer part of current clinical practice in some participating centers or has led to lowered enthusiasm in centers who were initially interested to participated in the trial.

Approximately 7 patients need to be screened to identify one with inherited thrombophilia [40]. Restrained by budget cuts even colleagues acknowledging the need for the study and willing to contribute can recruit only limited numbers of patients as those eligible are not identified because screening is not performed. Unless screening is performed in the context of patient care, a much higher study budget including costs of inherited thrombophilia screening of all women with unexplained recurrent miscarriage would be needed to overcome this problem.

Finally, once an eligible woman has been identified, she has to be informed of the study and sign consent to be enrolled. Although this may not sound as the greatest hurdle, the art of asking for informed consent is not easily mastered. Especially for a study like ALIFE2, where women

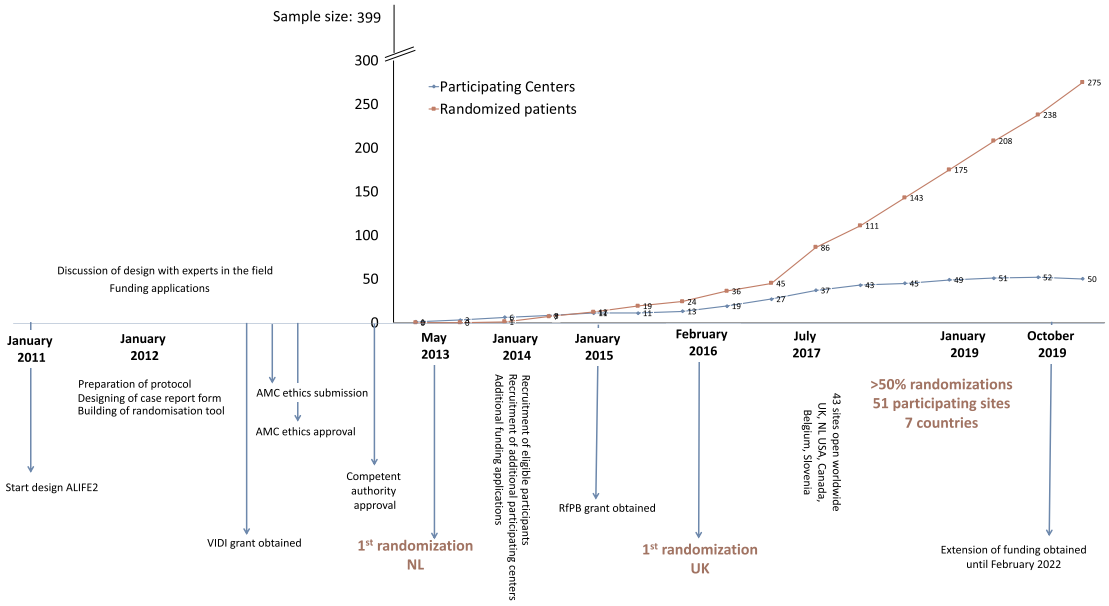


**Fig. 1.** Progress of the ALIFE2 study over time.
AMC: Amsterdam University Medical Centers – location Academic Medical Center, VIDI grant, personal grant for prof. Middeldorp from The Netherlands Organization for Health Research and Development (016.126.364); RfPB grant, UK National Institute for Health Research (NIHR), United Kingdom [PB-PG-1013-32011].

eligible for the study often are willing to do anything to improve their chance of a successful pregnancy, they may refuse participation for various reasons. Counselling is key and a good explanation of the study burden and potential benefits, but also of the scientific reasons why the study is designed and how only randomised trials will provide answers on whether therapies are effective, appear useful tools. Furthermore, some women consent to participation at a recurrent miscarriage consultation, but are not yet pregnant. It is important to stay in touch with these women, to ensure they remain aware of the study and are randomised as soon as they have a positive pregnancy test.

In the ALIFE2 study we register patients who are eligible, awaiting pregnancy and have signed informed consent. In this way, they can be randomised swiftly upon a positive pregnancy test. Interestingly, although women have declined participation for various reasons, so far in the Netherlands no eligible participant has declined to participate because of the 50% chance of being allocated to no treatment. In the UK recruitment is through NHS clinics, a small minority of women (< 2%) have declined to participate because they wanted to get the LMWH from the private sector. In the UK and North America, the striking feature of setting up this trial is that there has been more reluctance from clinicians than patients for this trial. The clinicians either believe that LMWH does not prevent miscarriage in acquired thrombophilia and thus they do not agree that the costs of thrombophilia screening is justified so do not allow screening or conversely, clinicians believe that LMWH does have a beneficial effect and prescribe LMWH with a positive screening result.

## 3. Current status of the ALIFE2 study

With the many obstacles identified and some overcome, there is also good news. Since the official launch of the study and the enrolment of the first participant on January 11 2013, the study is currently recruiting in 50 centers in 8 countries (number of centers (n) in the Netherlands $n = 8$, United Kingdom $n = 35$, United States of America $n = 2$, Canada $n = 1$, Australia n = 1, Austria n = 1, Belgium n = 1 and Slovenia n = 1). After obtaining funding (NIHR grant), the team at the University of Warwick set up the UK-ALIFE2 team alongside the NL-ALIFE2 team. The UK-team plans to recruit approximately 300 participants in the UK and the NL-team will coordinate all other participating (international) centers for the remaining 100 recruitments. Evaluating the enrolment rate per month, we have experienced an increase to approximately 5 randomizations per month in the past 4 months. As of January 31st 2020, a total of 275 women have been randomised in the trial, with an additional 118 registered eligible women who have provided informed consent and are awaiting pregnancy (Fig. 1).

Doubling of the number of participating centers, increasing awareness of the study and more involved collaboration between colleagues have doubled the enrolment rate. As of 2016, the ALIFE2 study is endorsed by INVENT-VTE, an international network established in 2015 aiming to accelerate clinical research in VTE [41]. With additional funding for participation of the UK obtained, 13 centers currently in set up and interest for the study is increasing globally, recruitment rates are expected to increase further within the near future. This increasing number of participating centers will not only add to the recruitment rate, but hopefully also improve dissemination and implementation of the study results, once obtained [42].

## 4. Conclusion

Designing and executing a multicenter trial is a huge operation, even if the trial addresses a clear gap of evidence and is broadly supported by clinicians and patients. This is especially true for investigator-initiated trials with limited funding. However, conducting such trials remains the only way forward on the road towards more evidence. Laying a solid foundation for the study amongst colleagues who will be requested to participate, in advance of the study, identifying those centers with dedicated investigators or trial offices, early recruitment of potential participating centers, and a constant and enthusiastic pursuit are key elements for success.

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